

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
30 November 2006 (30.11.2006)

PCT

(10) International Publication Number  
**WO 2006/127667 A1**

(51) International Patent Classification:  
*A61F 2/00* (2006.01)

(21) International Application Number:  
PCT/US2006/019848

(22) International Filing Date: 23 May 2006 (23.05.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
60/683,831 23 May 2005 (23.05.2005) US

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(81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**Published:**

- *with international search report*
- *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: FAST DEGRADING POLYMERS

(57) Abstract: The invention provides polyanhydrides that degrade in less than 60 hours following topical administration to deliver biologically active compounds.



**WO 2006/127667 A1**

## FAST DEGRADING POLYMERS

### Government Funding

The invention described herein was made with government support under  
5 Grant Number DE 13207 awarded by the National Institutes of Health. The  
United States Government has certain rights in the invention.

### Priority of Invention

This application claims priority from U.S. Provisional Application  
Number 60/683,831, filed 23 May 2005.

10

### Background of the Invention

Biodegradable polyanhydrides have been extensively researched for use  
as biomaterials for tissue engineering and drug delivery. Most polyanhydrides  
are biodegradable and biocompatible polymers that undergo hydrolysis *in vitro*  
and *in vivo* to release water-soluble biocompatible degradation products. These  
15 polymers completely degrade due to the hydrolytically labile nature of the  
anhydride bonds and their degradation rate can be controlled by manipulating the  
polymer composition. Polyanhydrides are predominantly surface eroding, which  
allows a controlled release, thus avoiding a burst release that can cause non-  
desirable side effects. All of these features make polyanhydrides useful for  
20 delivering biologically active compounds. See Uhrich, K.; et al.,  
*Macromolecules* **1995**, 28, 2184-2193; Uhrich, K.; et al., *J. Polym. Sci., Polym.*  
*Chem. Ed.* **1996**, 34, 1261-1269; Langer, R. *Acc. Chem. Res.* **2000**, 33, 94-101;  
Anastasiou, T.; Uhrich, K. *Macromolecules* **2000**, 33, 6217-6221; Mathiowitz,  
E., et al., *Nature* **1997**, 386, 410-414; Chasin, M.; Langer, R. *Biodegradable*  
25 *polymers as drug delivery systems*: New York, 1990; Brem, H., et al., *Lancet*  
**1995**, 345, 1008-1012; Hanes, J.; Chiba, M.; Langer, R. *Biomaterials* **1998**, 19,  
163-172; Leong, K., et al., *Biomaterials* **1986**, 7, 364-371; Leong, K., et al., *J.*  
*Biomed. Mater. Res.* **1986**, 20, 51-64; Sanders, A., et al., *Polym. Prepr.* **1999**, 40,  
888; Gopferich, A.; Tessmar, J. *Adv. Drug Del. Rev.* **2002**, 54, 911-931;  
30 Gopferich, A. *Biomaterials* **1996**, 17, 103-114; Whitaker-Brothers, K.; Uhrich,  
K. *J. Biomed. Mater. Res.* **2004**, 70A, 309-318; Prudencio, A.; Schmeltzer, R.  
C.; Uhrich, K. E. *Macromolecules* **2005**, 38, 6895-6901; Von Burkensroda, F.;  
Schedl, L.; Gopferich, A. *Biomaterials* **2002**, 23, 4221-4231; Tamada, J.;

Langer, R. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 552-556; and Quick, D.; and Macdonald, K.; Anseth, K. *J. Control. Rel.* **2004**, *97*, 333-343.

Previously, Erdmann et al. reported the synthesis of a poly(anhydride-ester) comprised of salicylic acid (SA) as a novel degradable biomaterial in which the drug, i.e. SA, is chemically incorporated into the polymer backbone and not attached as a side group or physically admixed. This unique system releases a high load of salicylic acid and sebacic acid upon hydrolysis of the ester and anhydride bonds in the backbone.

Phenolic compounds have been known for their wide biological activity, among which their antioxidant and antimicrobial activities stand out. Copolyesters containing natural non-toxic phenolic derivatives such as vanillic acid (VA) and syringic acid(SGA) were previously prepared and their mechanical properties studied (see Nagata, M., *J. Applied Polymer Sci.* **2000**, *78*, 2474-2481; Kricheldorf, H., et al., *Polymer* **1995**, *36*, 1697-1705; and Fan, J. et al., *J. Applied Polymer Sci.* **2006**, *100*, 1214-1221). However no study on the phenolic derivative release from these copolyesters was reported. See San Roman, J., et al., *J. Biomed. Mater. Res.* **1996**, *32*, 19-27; Sato, H., et al., *Biomater. Sci. Polymer. Ed.* **1991**, *2*, 1-13; Elvira, C., et al., *Polymer* **1999**, *40*, 6911-6924; Chafi, N.; Montheard, J.; Vergnaud, J. *Int J Pharm* **1989**, *52*, 203-211; Rivas, B., et al., *J. Membrane Sci.* **2001**, *192*, 187-191; and Elvira, C.; San Roman, J. *J. Mater. Sci.: Mater. in Med.* **1997**, *8*, 743-746.

In spite of the above disclosures, there remains a need for novel materials that can be applied to a wide range of applications. For example, there is a need for fast degrading polymers that can be used to deliver biologically active compounds via topical administration.

#### Summary of the Invention

In one embodiment the invention provides a composition of the invention which is a composition suitable for topical administration to an animal comprising a polyanhydride having a backbone that degrades within 60 hours of administration to provide a biologically active compound.

In another embodiment the invention provides a composition suitable for topical administration to an animal that comprises microspheres that degrade within 60 hours of administration, the microspheres comprising a polyanhydride having a backbone that comprises a hydroxy aryl carboxylic acid.

5 In another embodiment the invention provides a method for promoting an antioxidant, anticeptic, or antibacterial effect in an animal comprising topically administering a composition of the invention to the animal.

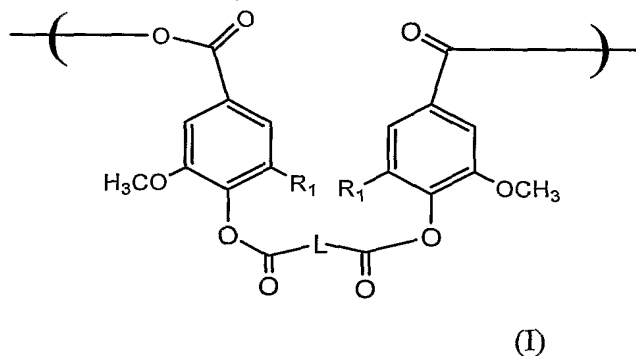
A method for administering a biologically active compound to an animal comprising topically applying to the animal a composition that comprises a  
10 polyanhydride having a backbone that degrades within 60 hours of applying to provide the biologically active compound.

In another embodiment the invention provides a composition of the invention for use in medical therapy.

In another embodiment the invention provides the use of a composition  
15 of the invention to prepare a medicament for promoting an antioxidant, anticeptic, or antibacterial effect when administered to an animal (e.g. a mammal).

In another embodiment the invention provides a polyanhydride that comprises units of the following formula (I):

20



wherein:

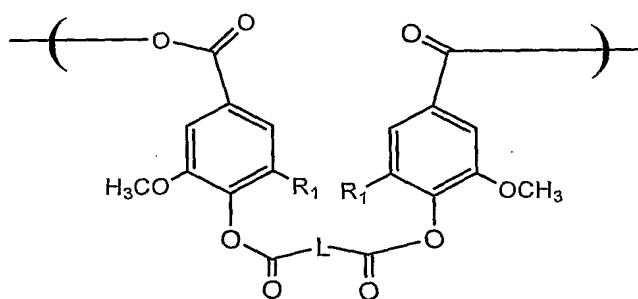
each  $R_1$  is independently H, or methoxy; and

25 L is a divalent, branched or unbranched, saturated or unsaturated, hydrocarbon chain, having from 1 to 20 carbon atoms, wherein the chain is

optionally substituted on carbon with one or more (e.g. 1, 2, 3, or 4) substituents selected from the group consisting of (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, (C<sub>1</sub>-C<sub>6</sub>)alkanoyl, (C<sub>1</sub>-C<sub>6</sub>)alkanoyloxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxycarbonyl, (C<sub>1</sub>-C<sub>6</sub>)alkylthio, azido, cyano, nitro, halo, hydroxy, oxo, carboxy, aryl, aryloxy, heteroaryl, and heteroaryloxy. In one specific embodiment of the invention the polyanhydride

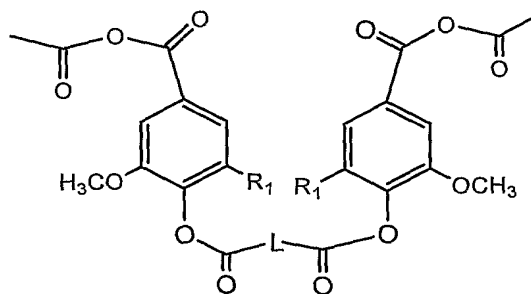
5 has a backbone that comprises repeating units of formula (I).

In another embodiment the invention provides a method for preparing a polyanhydride of formula (I):



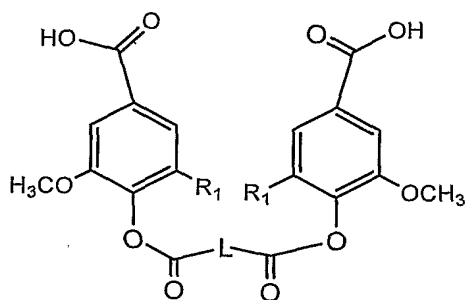
(I)

comprising polymerizing a corresponding compound of formula (II):



(II).

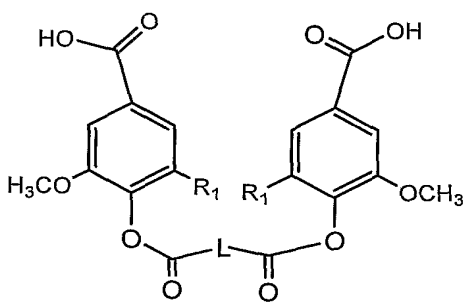
In another embodiment the invention provides a method for preparing a compound of formula (II) comprising acylating a corresponding diacid of formula (III):



(III).

In another embodiment the invention provides a compound of formula (III):

5



(III)

wherein:

each R<sub>1</sub> is independently H, or methoxy; and

L is a divalent, branched or unbranched, saturated or unsaturated, hydrocarbon chain, having from 1 to 20 carbon atoms, wherein the chain is optionally substituted on carbon with one or more (e.g. 1, 2, 3, or 4) substituents selected from the group consisting of (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, (C<sub>1</sub>-C<sub>6</sub>)alkanoyl, (C<sub>1</sub>-C<sub>6</sub>)alkanoyloxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxycarbonyl, (C<sub>1</sub>-C<sub>6</sub>)alkylthio, azido, cyano, nitro, halo, hydroxy, oxo, carboxy, aryl, aryloxy, heteroaryl, and heteroaryloxy; or a pharmaceutically acceptable salt thereof.

In another embodiment the invention provides a method for promoting an antioxidant, anticeptic, or antibacterial effect comprising topically administering a compound of formula (III) or a pharmaceutically acceptable salt thereof to an animal (e.g. mammal).

In another embodiment the invention provides a compound of formula (III) or a pharmaceutically acceptable salt thereof for use in medical therapy.

In another embodiment the invention provides the use of a compound of formula (III) or a pharmaceutically acceptable salt thereof to prepare a  
5 medicament for promoting an antioxidant, anticeptic, or antibacterial effect when administered to a mammal.

The invention also provides processes and intermediated disclosed herein that are useful for preparing polyanhydrides of formula (I).

#### Brief Description of the Figures

10 **Figure 1.** Free phenolic derivative release from poly(anhydride-esters) **1a-d** during hydrolytic degradation

**Figure 2.** Phenolic derivative-based poly(anhydride-esters) **1a-d** hydrolytic degradation.

**Figure 3.** Illustrates hydrolytic degradation of phenolic derivative-based  
15 poly(anhydride-esters), **1**.

**Figure 4.** Illustrates a synthetic scheme for preparing phenolic derivative-based poly(anhydride-esters), **1**.

#### Detailed Description

The synthesis of several poly(anhydride-esters) based on natural non-  
20 toxic aromatic hydroxy acids such as vanillic acid (VA) and syringic acid (SGA) with a high load of biologically active molecules in the polymer (from 67% up to 78% by weight) is described below. In addition, the degradation of the polymers (**1**) incorporating vanillic and syringic acid degraded into the phenolic hydroxy acid (**2**) and as well the carboxylic acid linker (**3**) (Figure 3) is described.

25 The relationship between the methoxy substitution on the aromatic ring and polymer composition, and the physical properties of the corresponding polymer were assessed with respect to delivery of the biologically active compounds. *In vitro* degradation studies were performed. Cytotoxicity and bacterial inhibition assays were conducted to assess potential application as an  
30 antibacterial polymeric materials. Thus, the degradation of these polymers and their cytotoxicity has been evaluated.

Specific values identified herein for radicals, substituents, and ranges, are for illustration only; they do not exclude other defined values or other values within defined ranges for the radicals and substituents

#### Degradation

5           The invention provides compositions that comprise polyanhydrides that degrade rapidly following administration to deliver one or more biologically active compounds. In one embodiment of the invention, the polyanhydride degrades within 60 hours of administration. The term “degrades” as used generally herein means that at least 60% of the anhydride bonds in the backbone  
10   of the polymer have hydrolyzed in the stated time period. In one specific embodiment of the invention, at least about 75% anhydride bonds in the backbone of the polymer have hydrolyzed in the stated time period. In another specific embodiment of the invention, at least about 90% anhydride bonds in the backbone of the polymer have hydrolyzed in the stated time period. In another  
15   specific embodiment of the invention, at least about 98% anhydride bonds in the backbone of the polymer have hydrolyzed in the stated time period. In another specific embodiment of the invention, all the anhydride bonds in the backbone of the polymer have hydrolyzed in the stated time period.

          The degradation rate for the polymers can be increased by incorporating  
20   electron donating groups into aromatic rings in the polymer backbone and by providing the polymers in the form of microspheres, which have a high surface area and thus allow for increased surface erosion.

#### Polymers of the Invention

          The biocompatible, biodegradable polyanhydrides of the invention are  
25   useful in a variety of applications where delivery of a biologically active compound is desired. Examples of such applications include, but are not limited to, medical, dental and cosmetic uses. The fast degrading polymers are particularly useful for delivering biologically active compounds by topical administration.

30           The polymers of the invention may be prepared in accordance with methods commonly employed in the field of synthetic polymers to produce a



variety of useful products with valuable physical and chemical properties. The polymers can be readily processed into pastes, films, coatings, microspheres and fibers, and may also be processed by compression molding and extrusion.

Polymers of the present invention can also be incorporated into oral  
5 formulations and into products such as skin moisturizers, cleansers, pads, plasters, lotions, creams, gels, ointments, solutions, shampoos, tanning products and lipsticks for topical application.

Preferably, the polymers of the invention comprise backbones wherein  
10 biologically active compounds and linker groups (L) are bonded together through ester linkages, thioester linkages, amide linkages, or a mixture thereof. Due to the presence of the ester, thioester, and/or amide linkages, the polymers can be hydrolyzed under physiological conditions to provide the biologically active compounds. Thus, the polymers of the invention can be particularly useful as a controlled release source for a biologically active compound, or as a medium for  
15 the localized delivery of a biologically active compound to a selected site.

The polyanhydrides can be prepared by the method described in Conix, Macromol. Synth., 2, 95-99 (1996) and by the methods described in International Patent Application Publication Number WO 02/009767. For example, a  
20 dicarboxylic acid can be acetylated in an excess of acetic anhydride at reflux temperatures followed by melt condensation of the resulting carboxylic acid anhydride at 180 °C for 2-3 hours to provide the polyanhydride polymers. The polymers can be isolated by precipitation into a suitable solvent (e.g. diethylether from methylene chloride). Useful polyanhydrides include both homopolymers and mixed polymers.

25 Polyanhydrides of the present invention typically have average molecular weights ranging between about 1500 daltons up to about 90,000 daltons, calculated by Gel Permeation Chromatography (GPC) relative to narrow molecular weight polystyrene standards. Some aromatic polyanhydrides have average molecular weights of about 1500 daltons, up to about 30,000 daltons  
30 calculated by Gel Permeation Chromatography (GPC) relative to narrow

molecular weight polystyrene standards. Other aromatic polyanhydrides have average molecular weights of about 3000 daltons, up to about 25,000 daltons.

#### Microspheres

Polymer microspheres can be fabricated by a solvent evaporation  
5 technique using an oil/water emulsion (Yeagy, B. et al., *J. Microencapsulation*  
**2006**, accepted). For example, the polymer is dissolved in methylene chloride  
(10 % wt/vol or 0.1 g in 1 mL) and added dropwise to (a 40-fold excess or 40  
mL) homogenized solution of 1 % wt/vol poly(vinyl alcohol), and the aqueous  
and organic phases are emulsified by homogenization (PowerGen 700, Fisher  
10 Scientific, Pittsburgh, PA) for 2 minutes at a speed setting of 5. The emulsified  
solution is then stirred at room temperature to evaporate the organic solvent.  
The polymer precipitates as the methylene chloride evaporates, and the hardened  
microspheres are vacuum filtered, washed several times (by centrifugation and  
resuspension) with deionized water and freeze dried (Freeze Dry  
15 System/Freezone 4.5, Labconco, Kansas City, MO).

#### Therapies

The polyanhydrides are designed to degrade quickly to allow for delivery  
of biologically active compounds over a period of hours to a few days.  
Accordingly, in one embodiment of the invention, a biologically active  
20 compound can be dispersed in the matrix of the polymer, and can be released  
upon degradation of the polymer. In another embodiment of the invention, a  
biologically active compound can be appended to a polymer of the invention (i.e.  
not in the backbone of the polymer) with bonds that hydrolyze to release the  
biologically active compound under predetermined conditions. In another  
25 embodiment of the invention, the polymer backbone itself includes groups that  
provide one or more biologically active compounds upon degradation (e.g.  
hydrolysis) of the backbone. Combinations of the above embodiments of the  
invention are also possible. For example, the polymer backbone itself may  
include groups that provide one or more biologically active compounds upon  
30 degradation (e.g. hydrolysis) of the backbone, and there may also be biologically

active compounds appended to the polymer backbone or dispersed in the matrix of the polymer.

#### Combination Therapies

The invention also provides compositions and methods that are useful for delivering two or more biologically active compounds. For example, in one embodiment of the invention, two or more biologically active compounds are dispersed within the polymer matrix, and can be released upon degradation of the polymer. In another embodiment of the invention, the polymer backbone itself includes groups that provide two or more biologically active compounds upon degradation (e.g. hydrolysis) of the backbone. Combinations of the above embodiments of the invention are also possible. For example, the polymer backbone itself may include groups that provide one or more biologically active compounds upon degradation (e.g. hydrolysis) of the backbone and there may also be other biologically active compounds dispersed in the matrix of the polymer. Alternatively, two polymers of the invention, each with a different biologically active compound in the backbone, can be administered together in a single composition.

#### Biologically Active Compounds

The term "biologically active compound" includes agents that provide a therapeutically desirable effect when administered to an animal (e.g., a mammal, such as a human). Therapeutic agents that can be included in the compositions described herein include analgesics, anesthetics, anti-Parkinson's agents, anti-infectives, antiacne agents, antibiotics, anticholinergics, anticoagulants, anticonvulsants, antidiabetic agents, antidyskinetics, antifibrotic agents, antifibrotics, antifungal agents, antiglaucoma agents, anti-inflammatory agents, antioxidants, antineoplastics, antiosteoporotics, antipagetics, antispuratics, antipyretics, antiseptics/disinfectants, antithrombotics, bone resorption inhibitors, calcium regulators, cardioprotective agents, cardiovascular agents, central nervous system stimulants, cholinesterase inhibitors, contraceptives, deodorants, dopamine receptor agonists, erectile dysfunction agents, fertility agents, gastrointestinal agents, gout agents, hormones, hypnotics,

immunomodulators, immunosuppressives, keratolytics, migraine agents, motion sickness agents, muscle relaxants, nucleoside analogs, obesity agents, ophthalmic agents, osteoporosis agents, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sclerosing agents, sedatives, skin and mucous membrane agents, smoking cessation agents, sympatholytics, synthetic antibacterial agents, ultraviolet screening agents, urinary tract agents, vaginal agents, and vasodilators (see Physicians' Desk Reference, 55 ed., 2001, Medical Economics Company, Inc., Montvale, New Jersey, pages 201-202).

10           The biologically active compounds can also comprise functional groups (including hydroxy groups, mercapto groups, amine groups, and carboxylic acids, as well as others) that can be used to modify the properties of the polymer (e.g. for branching, for cross linking, for appending other molecules (e.g. another biologically active compound) to the polymer, for changing the solubility of the polymer, or for effecting the biodistribution of the polymer). Lists of therapeutic agents can be found, for example, in: Physicians' Desk Reference, 55 ed., 2001, Medical Economics Company, Inc., Montvale, New Jersey; USPN Dictionary of USAN and International Drug Names, 2000, The United States Pharmacopeial Convention, Inc., Rockville, Maryland; and The Merck Index, 12 ed., 1996, Merck & Co., Inc., Whitehouse Station, New Jersey. One skilled in the art can readily select therapeutic agents that possess the necessary functional groups for incorporation into the polymers of the invention from these lists.

Examples of anti-bacterial compounds suitable for use in the present invention include, but are not limited to, 4-sulfanilamidosalicylic acid, acediasulfone, amfenac, amoxicillin, ampicillin, apalcillin, apicycline, aspoxicillin, aztreonam, bambermycin(s), biapenem, carbenicillin, carumonam, cefadroxil, cefamandole, cefatrizine, cefbuperazone, cefclidin, cefdinir, cefditoren, cefepime, cefetamet, cefixime, cefmenoxime, cefminox, cefodizime, cefonicid, cefoperazone, ceforanide, cefotaxime, cefotetan, cefotiam, cefozopran, cefpimizole, cefpiramide, cefpirome, cefprozil, cefroxadine, ceftazidime, cefteteram, ceftibuten, ceftriaxone, cefuzonam, cephalixin, cephaloglycin,

cephalosporin C, cephradine, ciprofloxacin, clinafloxacin, cyclacillin, enoxacin, epicillin, flomoxef, grepafloxacin, hetacillin, imipenem, lomefloxacin, lymecycline, meropenem, moxalactam, mupirocin, nadifloxacin, norfloxacin, panipenem, pazufloxacin, penicillin N, pipemidic acid, quinacillin, ritipenem, 5 salazosulfadimidine, sparfloxacin, succisulfone, sulfachrysoidine, sulfaloxic acid, teicoplanin, temafloxacin, temocillin, ticarcillin, tigemonam, tosufloxacin, trovafloxacin, vancomycin, and the like.

Examples of anti-fungal compounds suitable for use in the present invention include, but are not limited to amphotericin B, azaserine, candididin(s), 10 lucensomycin, natamycin, nystatin, and the like.

Examples of anti-neoplastic compounds suitable for use in the present invention include, but are not limited to 6-diazo-5-oxo-L-norleucine, azaserine, carzinophillin A, denopterin, edatrexate, eflornithine, melphalan, methotrexate, mycophenolic acid, podophyllinic acid 2-ethylhydrazide, pteropterin, 15 streptonigrin, Tomudex® (N-((5-(((1,4-Dihydro-2-methyl-4-oxo-6-quinazolinyl)methyl)methylamino)-2-thienyl)carbonyl)-L-glutamic acid), ubenimex, and the like.

Examples of anti-thrombotic compounds for use in the present invention include, but are not limited to, argatroban, iloprost, lamifiban, taprostene, 20 tirofiban and the like.

Examples of immunosuppressive compounds suitable for use in the present invention include, but are not limited to bucillamine, mycophenolic acid, procodazole, romurtide, ubenimex and the like.

Examples of NSAID compounds suitable for use in the present invention include, but are not limited to 3-amino-4-hydroxybutyric acid, aceclofenac, 25 alminoprofen, bromfenac, bumadizon, carprofen, diclofenac, diflunisal, enfenamic acid, etodolac, fendosal, flufenamic acid, gentisic acid, meclofenamic acid, mefenamic acid, mesalamine, niflumic acid, olsalazine oxaceprol, S-adenosylmethionine, salicylic acid, salsalate, sulfasalazine, tolfenamic acid, and 30 the like.

Examples of anti-oxidant compounds suitable for use in the present invention include, vanillic acid, syringic acid, *p*-coumaric acid, caffeic acid, gallic acid, ferulic acid, sinapic acid, protocatechuic acid, and *p*-hydroxybenzoic acid.

- 5 Biologically active compounds that can be incorporated into the backbone of degradable polymers as described herein typically have molecular weights of approximately 1,000 daltons or less. Additionally, if the the biologically active compound is to be incorporated into the backbone of the polyanhydride, it must contain within its molecular structure one carboxylic acid  
10 group and at least one other functional group selected from carboxylic acid (-COOH), amine (-NHR), thiol (-SH), alcohol (-OH) or phenol (-Ph-OH).

- A specific biologically active compound is 3-amino-4-hydroxybutyric acid, 6-diazo-5-oxo-L-norleucine, aceclofenac, acediasulfone, alminoprofen, amfenac, amoxicillin, amphotericin B, ampicillin, apalcillin, apicycline,  
15 aspoxicillin, azaserine, aztreonam, bambarmycin(s), biapenem, bromfenac, buccillamine, bumadizon, candicidin(s), carbenicillin, carprofen, carumonam, carzinophillin A, cefadroxil, cefamandole, cefatrizine, cefbuperazone, cefclidin, cefdinir, cefditoren, cefepime, cefetamet, cefixime, cefmenoxime, cefminox, cefodizime, cefonicid, cefoperazone, ceforanide, cefotaxime, cefotetan, cefotiam,  
20 cefozopran, cefpimizole, cefpiramide, cefpirome, cefprozil, cefroxadine, ceftazidime, cefteram, ceftibuten, ceftriaxone, cefuzonam, cephalixin, cephaloglycin, cephalosporin C, cephradine, ciprofloxacin, clinafloxacin, cyclacillin, denopterin, diclofenac, edatrexate, eflornithine, enfenamic acid, enoxacin, epicillin, etodolac, flomoxef, flufenamic acid, grepafloxacin,  
25 hetacillin, imipenem, lomefloxacin, lucensomycin, lymecycline, meclofenamic acid, mefenamic acid, melphalan, meropenem, methotrexate, moxalactam, mupirocin, mycophenolic acid, mycophenolic acid, nadifloxacin, natamycin, niflumic acid, norfloxacin, nystatin, oxaceprol, panipenem, pazufloxacin, penicillin N, pipemidic acid, podophyllinic acid 2-ethylhydrazide, procodazole,  
30 pteropterin, quinacillin, ritipenem, romurtide, S-adenosylmethionine, salazosulfadimidine, sparfloxacin, streptonigrin, succisulfone, sulfachrysoidine,

sulfaloxic acid, teicoplanin, temafloxacin, temocillin, ticarcillin, tigemonam, tolfenamic acid, Tomudex® (N-((5-(((1,4-Dihydro-2-methyl-4-oxo-6-quinazolinyl)methyl)methylamino)-2-thienyl)carbonyl)-L-glutamic acid), tosufloxacin, trovafloxacin, ubenimex or vancomycin.

## 5 Linking Group "L"

The nature of the linking group "L" in a polymer of the invention is not critical provided the polymer of the invention possesses acceptable mechanical properties and release kinetics for the selected therapeutic application. The linking group L is typically a divalent organic radical having a molecular weight  
10 of from about 25 daltons to about 400 daltons. More preferably, L has a molecular weight of from about 40 daltons to about 200 daltons.

The linking group L typically has a length of from about 5 angstroms to about 100 angstroms using standard bond lengths and angles. More preferably, the linking group L has a length of from about 10 angstroms to about 50  
15 angstroms.

The linking group may be biologically inactive, or may itself possess biological activity. The linking group can also comprise other functional groups (including hydroxy groups, mercapto groups, amine groups, carboxylic acids, as well as others) that can be used to modify the properties of the polymer (e.g. for  
20 branching, for cross linking, for appending other molecules (e.g. another biologically active compound) to the polymer, for changing the solubility of the polymer, or for effecting the biodistribution of the polymer).

A specific value for L is a divalent, branched or unbranched, saturated or unsaturated, hydrocarbon chain, having from 1 to 20 carbon atoms, wherein the  
25 chain is optionally substituted on carbon with one or more (e.g. 1, 2, 3, or 4) substituents selected from the group consisting of (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, (C<sub>1</sub>-C<sub>6</sub>)alkanoyl, (C<sub>1</sub>-C<sub>6</sub>)alkanoyloxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxycarbonyl, (C<sub>1</sub>-C<sub>6</sub>)alkylthio, azido, cyano, nitro, halo, hydroxy, oxo, carboxy, aryl, aryloxy, heteroaryl, and heteroaryloxy.

30 Another specific value for L is a divalent, branched or unbranched, saturated or unsaturated, hydrocarbon chain, having from 1 to 20 carbon atoms,

wherein one or more (e.g. 1, 2, 3, or 4) of the carbon atoms is optionally replaced by (-O-) or (-NR-).

A more specific value for L is a divalent, branched or unbranched, saturated or unsaturated, hydrocarbon chain, having from 3 to 15 carbon atoms, wherein one or more (e.g. 1, 2, 3, or 4) of the carbon atoms is optionally replaced by (-O-) or (-NR-), and wherein the chain is optionally substituted on carbon with one or more (e.g. 1, 2, 3, or 4) substituents selected from the group consisting of (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, (C<sub>1</sub>-C<sub>6</sub>)alkanoyl, (C<sub>1</sub>-C<sub>6</sub>)alkanoyloxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxycarbonyl, (C<sub>1</sub>-C<sub>6</sub>)alkylthio, azido, cyano, nitro, halo, hydroxy, oxo, carboxy, aryl, aryloxy, heteroaryl, and heteroaryloxy.

Another more specific value for L is a divalent, branched or unbranched, saturated or unsaturated, hydrocarbon chain, having from 3 to 15 carbon atoms, wherein one or more (e.g. 1, 2, 3, or 4) of the carbon atoms is optionally replaced by (-O-) or (-NR-).

Another more specific value for L is a divalent, branched or unbranched, saturated or unsaturated, hydrocarbon chain, having from 3 to 15 carbon atoms.

Another more specific value for R<sup>2</sup> is a divalent, branched or unbranched, hydrocarbon chain, having from 3 to 15 carbon atoms.

Another more specific value for L is a divalent, branched or unbranched, hydrocarbon chain, having from 6 to 10 carbon atoms.

Another more specific value for L is a divalent hydrocarbon chain having 7, 8, or 9 carbon atoms.

Another more specific value for L is a divalent hydrocarbon chain having 8 carbon atoms.

Another more specific value for L is a divalent, branched or unbranched, hydrocarbon chain, having from 4 to 8 carbon atoms.

Another more specific value for L is -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-.

The compositions of the invention can be incorporated into a variety of products that can be used to topically deliver biologically active compounds. For example, the compositions of the invention can be incorporated into deodorants, baby care products (e.g. diapers and wipes), cosmetics, feminine hygiene



products, hair care products (e.g. shampoos, and conditioners), household cleaners (e.g. soaps and wipes) laundry products and fabric care products (e.g. soaps, fabric softeners) paper products (e.g. wipes), personal cleansing products (e.g. soaps) and skin care products (e.g. moisturizers).

5           For topical administration, it will generally be desirable to administer the polymers to the skin as compositions or formulations, in combination with a dermatologically acceptable carrier, which may be a solid or a liquid.

          Useful solid carriers include finely divided solids such as talc, clay, microcrystalline cellulose, silica, alumina and the like. Useful liquid carriers  
10       include water, alcohols or glycols or water-alcohol/glycol blends, in which the present compounds can be dissolved or dispersed at effective levels, optionally with the aid of non-toxic surfactants. Adjuvants such as fragrances and additional antimicrobial agents can be added to optimize the properties for a given use. The resultant liquid compositions can be applied from absorbent  
15       pads, used to impregnate bandages and other dressings, or sprayed onto the affected area using pump-type or aerosol sprayers.

          Thickeners such as synthetic polymers, fatty acids, fatty acid salts and esters, fatty alcohols, modified celluloses or modified mineral materials can also be employed with liquid carriers to form spreadable pastes, gels, ointments,  
20       soaps, and the like, for application directly to the skin of the user.

          Examples of useful dermatological compositions which can be used to deliver the compounds of formula I to the skin are known to the art; for example, see Jacquet et al. (U.S. Pat. No. 4,608,392), Geria (U.S. Pat. No. 4,992,478), Smith et al. (U.S. Pat. No. 4,559,157) and Wortzman (U.S. Pat. No. 4,820,508).

25           Pharmaceutically acceptable salts may be obtained using standard procedures well known in the art, for example by reacting a sufficiently basic compound such as an amine with a suitable acid affording a physiologically acceptable anion. Alkali metal (for example, sodium, potassium or lithium) or alkaline earth metal (for example calcium) salts of carboxylic acids can also be  
30       made.

Useful dosages of the biologically active compound I can be determined by comparing their *in vitro* activity, and *in vivo* activity in animal models. Methods for the extrapolation of effective dosages in mice, and other animals, to humans are known to the art; for example, see U.S. Pat. No. 4,938,949.

5           Generally, the concentration of biologically active compound in a liquid composition, such as a lotion, will be from about 0.1-25 wt-%, preferably from about 0.5-10 wt-%. The concentration in a semi-solid or solid composition such as a gel or a powder will be about 0.1-5 wt-%, preferably about 0.5-2.5 wt-%.

          The invention will now be illustrated by the following non-limiting  
10   Examples.

### EXAMPLES

#### Example 1.

**Materials and Methods.** Tetrahydrofuran (THF), pyridine, acetic anhydride, methylene chloride, and diethyl ether were purchased from Fisher  
15   (Fair Lawn, NJ). All other fine chemicals and solvents were obtained from Aldrich (Milwaukee, WI) and used as received.

          Proton nuclear magnetic resonance ( $^1\text{H}$  NMR) spectra were recorded on a Varian 300 MHz spectrometer. The samples (5-10 mg) were dissolved in a deuterated solvent ( $\text{DMSO}-d_6$ ), which was also used as the internal reference.  
20   Infrared (IR) spectra were measured on a Thermo Nicolet/Avatar 360 FT IR spectrometer, by depositing samples onto NaCl plates (if liquid) or solvent-casting samples from methylene chloride onto NaCl plates (if solid).

          Weight-averaged molecular weights (Mw) were determined by gel permeation chromatography (GPC) on a Perkin-Elmer liquid chromatography  
25   system consisting of a Series 200 refractive index detector, a Series 200 LC pump, and an ISS 200 advanced sample processor. A Dell OptiPlex GX110 computer running Perkin-Elmer TurboChrom 4 software was used for data collection and processing, and to automate the analysis via Perkin-Elmer Nelson 900 Series Interface and 600 Series Link. Polymers were dissolved in methylene  
30   chloride (5 mg/mL) and filtered through 0.45  $\mu\text{m}$  poly(tetrafluoroethylene) (PTFE) syringe filters (Whatman, Clifton, NJ) before elution. Samples were

resolved on a Jordi divinylbenzene mixed-bed GPC column (7.8 x 300 mm) (Alltech Associates, Deerfield, IL) at 25 °C, with methylene chloride as eluent at a flow rate of 0.5 mL/min. Molecular weights were calibrated relative to narrow molecular weight polystyrene standards (Polysciences, Dorval, Canada).

5 Thermal analyses were performed on a Perkin-Elmer system consisting of Pyris 1 DSC and TGA 7 analyzers with TAC 7/DX instrument controllers. Perkin-Elmer Pyris software was used for data collection on a Dell OptiPlex GX110 computer. For DSC, samples (5 mg) were heated under dry nitrogen gas. Data were collected at heating and cooling rates of 10 °C/min with a two-cycle  
10 minimum. Glass transition temperatures were calculated as half Cp extrapolated. For TGA, samples (10 mg) were heated under dry nitrogen gas. Data were collected at a heating rate of 10 °C/min. Decomposition temperatures were defined as the onset of decomposition.

Elemental analyses were provided by QTI (Whitehouse, NJ). Melting  
15 points below 200 °C were obtained with a Mel-Temp apparatus at a heating rate of 1 °C per minute, while those above 200 °C were determined on the Pyris 1 DSC (see above).

Sessile-drop contact angles of phosphate buffer solution on polymer disks were measured using an automated Ramé-hart goniometer (Model 250, Netcong,  
20 NJ) with DROPimage Advanced software. Angles were measured on 3 different disks for each polymer and an averaged value was taken. Polymers (150 mg) disks were prepared by pressing ground polymers ( $\sim 150 \pm 5$  mg) into 13 mm diameter x 1 mm thick disks in an IR pellet die (International Crystal Laboratories, Garfield, NJ) with a bench-top hydraulic press (Carver model M,  
25 Wabash, IN by applying a pressure of 5000 psi for 5 min.

Vanillic acid (VA) and syringic acid (SGA) concentrations in the degradation media were determined on a Perkin-Elmer HPLC system consisting of a 785A absorbance detector (Applied Biosystems, Foster City, CA), a Series 200 quaternary LC pump, and an ISS 200 autosampler. A Dell OptiPlex GX110  
30 computer running Perkin-Elmer TurboChrom 4 software was used for data collection and processing, and to automate the analysis via Perkin-Elmer Nelson

900 Series Interface and 600 Series Link. Degradation media was filtered through 0.45  $\mu\text{m}$  poly(tetrafluoroethylene) (PTFE) syringe filters (Whatman, Clifton, NJ) before elution. Samples were resolved on a Zorbax C-8 reverse-phase column (4.6 x 150 mm) (Agilent, Foster City, CA) at 25 °C using a mixture of methanol:DDW:TFA 50:49.05:0.05 v/v/v as eluent at a flow rate of 1.0 mL/min to determine VA with UV detection at 251 nm and SGA with UV detection at 261 nm.

**Poly(anhydride-esters) Precursors: Diacid Synthesis (5).** Diacids were prepared by reaction of vanillic acid (**2a**) or syringic acid (**2b**) with the appropriate acyl chloride in the presence of a base (pyridine). The preparation of **5a** is provided as an example. Vanillic acid (**2a**) (3.6 g, 21 mmol) was dissolved in THF (40 mL) and pyridine (5.2 mL, 64 mmol). Adipoyl chloride (**4a**) (1.6 mL, 11 mmol) dissolved in tetrahydrofuran (10 mL) was added dropwise over 5 minutes to the stirring reaction mixture at room temperature to afford a suspension. The reaction was stirred for 2 h at room temperature, poured over water (400 mL) and acidified to pH~2 using concentrated hydrochloric acid while stirring. The off-white solid (diacid, **5a**) that formed was isolated by vacuum filtration, washed with water (3x100mL) and dried overnight under vacuum at room temperature.

**1,6-bis(3-methoxy-1,4-carboxyphenoxy)-hexanoate (5a).** Yield: 73% (white powder).  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  7.60 (m, 4H, ArH), 7.20 (d, 2H, ArH), 3.80 (s, 6H, CH<sub>3</sub>), 2.65 (t, 4H, CH<sub>2</sub>), 1.75 (t, 4H, CH<sub>2</sub>). IR (NaCl,  $\text{cm}^{-1}$ ): 3600-3100 (OH, COOH), 1750 (C=O, ester), 1685 (C=O, COOH). Anal. Calcd.: C, 59.2%; H, 5.0%; O, 35.8%. Found: C, 58.8%; H, 4.9%; O, 36.3%; mp: 205-206 °C.

**1,10-bis(3-methoxy-1,4-carboxyphenoxy)-decanoate (5b).** Yield: 77% (white powder).  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  7.60 (m, 4H, ArH), 7.20 (d, 2H, ArH), 3.80 (s, 6H, CH<sub>3</sub>), 2.60 (t, 4H, CH<sub>2</sub>), 1.65 (m, 4H, CH<sub>2</sub>), 1.40 (m, 8H, CH<sub>2</sub>). IR (NaCl,  $\text{cm}^{-1}$ ): 3650-3100 (OH, COOH), 1760 (C=O, ester), 1695 (C=O, COOH). Anal. Calcd.: C, 62.2%; H, 6.0%; O, 31.8%. Found: C, 61.8%; H, 6.1%; O, 32.1%; mp: 176-178 °C.

**1,6-bis(3,5-dimethoxy-1,4-carboxyphenoxy)-hexanoate (5c).** Yield: 70% (white powder).  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  7.25 (s, 4H, ArH), 3.80 (s, 12H,  $\text{CH}_3$ ), 2.65 (t, 4H,  $\text{CH}_2$ ), 1.75 (t, 4H,  $\text{CH}_2$ ). IR ( $\text{NaCl}$ ,  $\text{cm}^{-1}$ ): 3650-3100 (OH, COOH), 1760 ( $\text{C}=\text{O}$ , ester), 1680 ( $\text{C}=\text{O}$ , COOH). Anal. Calcd.: C, 56.9%; H, 5.2%; O, 37.9%. Found: C, 56.6%; H, 5.1%; O, 38.3%; mp: 227-230 °C.

**1,10-bis(3,5-dimethoxy-1,4-carboxyphenoxy)-decanoate (5d).** Yield: 79% (white powder).  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  7.25 (s, 4H, ArH), 3.80 (s, 12H,  $\text{CH}_3$ ), 2.55 (t, 4H,  $\text{CH}_2$ ), 1.65 (m, 4H,  $\text{CH}_2$ ), 1.35 (m, 8H,  $\text{CH}_2$ ). IR ( $\text{NaCl}$ ,  $\text{cm}^{-1}$ ): 3600-3100 (OH, COOH), 1765 ( $\text{C}=\text{O}$ , ester), 1695 ( $\text{C}=\text{O}$ , COOH). Anal. Calcd.: C, 59.8%; H, 6.1%; O, 34.1%. Found: C, 59.5%; H, 6.2%; O, 34.3%; mp: 193-195 °C.

**Monomer Synthesis (6).** The diacid (5) (3.0 g) was activated with stirring in an excess of acetic anhydride (50 mL) at room temperature until the initial suspension becomes a clear solution (approximately 3-12 h). The excess acetic anhydride is removed by rotoevaporation at room temperature under vacuum to afford the monomer.

**1,6-bis(3-methoxy-1,4-carboxyphenoxy)-hexanoate Monomer (6a).** Yield: quantitative (orangish oil).  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  7.60 (m, 4H, ArH), 7.20 (d, 2H, ArH), 3.80 (s, 6H,  $\text{CH}_3$ ), 2.65 (t, 4H,  $\text{CH}_2$ ), 2.10 (s, 6H,  $\text{CH}_3$ ), 1.75 (t, 4H,  $\text{CH}_2$ ). IR ( $\text{NaCl}$ ,  $\text{cm}^{-1}$ ): 1810, 1735 ( $\text{C}=\text{O}$ , anhydride), 1760 ( $\text{C}=\text{O}$ , ester).  $T_d = 274$  °C.

**1,10-bis(3-methoxy-1,4-carboxyphenoxy)-decanoate Monomer (6b).** Yield: quantitative (orangish oil).  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  7.60 (m, 4H, ArH), 7.20 (d, 2H, ArH), 3.80 (s, 6H,  $\text{CH}_3$ ), 2.65 (t, 4H,  $\text{CH}_2$ ), 2.10 (s, 6H,  $\text{CH}_3$ ), 1.65 (m, 4H,  $\text{CH}_2$ ), 1.35 (m, 8H,  $\text{CH}_2$ ). IR ( $\text{NaCl}$ ,  $\text{cm}^{-1}$ ): 1820, 1735 ( $\text{C}=\text{O}$ , anhydride), 1770 ( $\text{C}=\text{O}$ , ester).  $T_d = 348$  °C.

**1,6-bis(3,5-dimethoxy-1,4-carboxyphenoxy)-hexanoate Monomer (6c).** Yield: quantitative (white powder).  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  7.35 (s, 4H, ArH), 3.85 (s, 12H,  $\text{CH}_3$ ), 2.70 (t, 4H,  $\text{CH}_2$ ), 2.20 (s, 6H,  $\text{CH}_3$ ), 1.80 (t, 4H,  $\text{CH}_2$ ). IR ( $\text{NaCl}$ ,  $\text{cm}^{-1}$ ): 1810, 1720 ( $\text{C}=\text{O}$ , anhydride), 1765 ( $\text{C}=\text{O}$ , ester).  $T_d = 290$  °C.

**1,10-bis(3,5-dimethoxy-1,4-carboxyphenoxy)-decanoate Monomer**

(6d). Yield: quantitative (white powder).  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  7.30 (s, 4H, ArH), 3.80 (s, 12H,  $\text{CH}_3$ ), 2.55 (t, 4H,  $\text{CH}_2$ ), 2.20 (s, 6H,  $\text{CH}_3$ ), 1.65 (m, 4H,  $\text{CH}_2$ ), 1.35 (m, 8H,  $\text{CH}_2$ ). IR ( $\text{NaCl}$ ,  $\text{cm}^{-1}$ ): 1810, 1725 ( $\text{C}=\text{O}$ , anhydride), 1765 (C=O, ester).  $T_d = 351\text{ }^\circ\text{C}$ .

**Polymer Synthesis (1).** Monomer (6) (3.0 g) was placed in a 100 mL two-necked round-bottom flask with 24/40 joints with a vacuum joint in one neck and a Teflon vacuum-stirring adapter in the other. The reaction flask was heated up to  $160\text{ }^\circ\text{C}$  using a temperature controller (Cole Parmer) in a silicone oil bath under high vacuum ( $<2\text{ mm Hg}$ ). During this time, the melt was actively stirred at  $\sim 100\text{ rpm}$  by an overhead stirrer (T-line Laboratory Stirrer, Talboys Engineering, Montrose, PA). Polymerization was complete when the viscosity of the melt remained constant and/or solidified (4 h). The polymer was cooled to room temperature, and isolated by precipitation in methylene chloride/diethyl ether (5 mL/100 mL).

**Poly[1,6-bis(3-methoxy-1,4-carboxyphenoxy)-hexanoate] (1a).** Yield: quantitative (off-white solid).  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  7.80 (m, 4H, ArH), 7.35 (d, 2H, ArH), 3.85 (s, 6H,  $\text{CH}_3$ ), 2.70 (t, 4H,  $\text{CH}_2$ ), 1.75 (t, 4H,  $\text{CH}_2$ ). IR ( $\text{NaCl}$ ,  $\text{cm}^{-1}$ ): 1790, 1720 ( $\text{C}=\text{O}$ , anhydride), 1765 ( $\text{C}=\text{O}$ , ester).  $M_w = 63100$ , PDI = 1.3.  $T_d = 268\text{ }^\circ\text{C}$ ,  $T_g = 59\text{ }^\circ\text{C}$ . Contact Angle:  $60^\circ$ .

**Poly[1,10-bis(3-methoxy-1,4-carboxyphenoxy)-decanoate] (1b).** Yield: quantitative (off-white solid).  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  7.75 (m, 4H, ArH), 7.30 (d, 2H, ArH), 3.85 (s, 6H,  $\text{CH}_3$ ), 2.60 (t, 4H,  $\text{CH}_2$ ), 1.60 (m, 4H,  $\text{CH}_2$ ), 1.30 (m, 8H,  $\text{CH}_2$ ). IR ( $\text{NaCl}$ ,  $\text{cm}^{-1}$ ): 1795, 1725 ( $\text{C}=\text{O}$ , anhydride), 1765 ( $\text{C}=\text{O}$ , ester).  $M_w = 88800$ , PDI = 1.3.  $T_d = 325\text{ }^\circ\text{C}$ ,  $T_g = 37\text{ }^\circ\text{C}$ . Contact Angle:  $71^\circ$ .

**Poly[1,6-bis(3,5-dimethoxy-1,4-carboxyphenoxy)-hexanoate] (1c).** Yield: quantitative (white solid).  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  7.45 (s, 4H, ArH), 3.85 (s, 12H,  $\text{CH}_3$ ), 2.65 (t, 4H,  $\text{CH}_2$ ), 1.80 (t, 4H,  $\text{CH}_2$ ). IR ( $\text{NaCl}$ ,  $\text{cm}^{-1}$ ): 1795, 1720 ( $\text{C}=\text{O}$ , anhydride), 1765 ( $\text{C}=\text{O}$ , ester).  $M_w = 12500$ , PDI = 2.0.  $T_d = 289\text{ }^\circ\text{C}$ ,  $T_g = 86\text{ }^\circ\text{C}$ . Contact Angle:  $60^\circ$ .

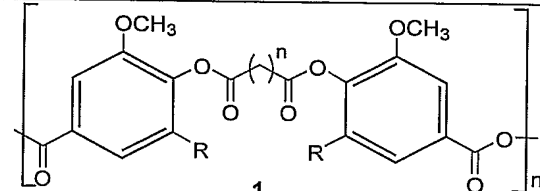
**Poly[1,10-bis(3,5-dimethoxy-1,4-carboxyphenoxy)-decanoate] (1d).**

Yield: quantitative (white solid).  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  7.45 (s, 4H, ArH), 3.80 (s, 12H,  $\text{CH}_3$ ), 2.60 (t, 4H,  $\text{CH}_2$ ), 1.65 (m, 4H,  $\text{CH}_2$ ), 1.35 (m, 8H,  $\text{CH}_2$ ). IR ( $\text{NaCl}$ ,  $\text{cm}^{-1}$ ): 1790, 1725 ( $\text{C}=\text{O}$ , anhydride), 1765 ( $\text{C}=\text{O}$ , ester).  $M_w = 34300$ ,  
5 PDI = 1.9.  $T_d = 335\text{ }^\circ\text{C}$ ,  $T_g = 79\text{ }^\circ\text{C}$ . Contact Angle:  $75^\circ$ .

Poly(anhydride-esters) comprised of two phenolic derivatives (**1**) were prepared by melt-condensation polymerization methods as outlined in Figure 4.

Polymer precursors or diacids (**5**) were synthesized according to previously described methods in yields ranging from 67 to 78% (see Uhrich, K.  
10 E. *Macromolecules* **2005**, 38, 6895-6901; Schmeltzer, R., et al., *Polym. Bull.* **2003**, 49, 441-448; and Fan, J., et al., *J Applied Polymer Science* **2006**, 100, 1214-1221). Diacids (**5**) were activated into the monomers (**6**) with acetic anhydride and ultimately melt-polymerized at  $160\text{ }^\circ\text{C}$  under vacuum ( $<2\text{ mmHg}$ ). The polymerization temperature was chosen based on the monomer  
15 decomposition temperature and polymerization time (4h) upon solidification of the melt. The chemical incorporation of vanillic acid (VA) and syringic acid (SGA) into the polymeric backbone allowed a loading efficiency ranging from 67 up to 78 wt % (Table 1).

The polymers had molecular weights of 12,500-88,800, with the higher  
20 methoxy-substituted phenolic derivative-based polymers (**1c,d**) yielding the lowest molecular weights as shown in Table 1. Molecular weights significantly increased with the alkyl chain length of the compound linking the two phenolic derivative units. Similarly, alkyl linker chain length influenced polymer thermal properties, increasing decomposition temperature ( $T_d$ ) and glass transition  
25 temperature ( $T_g$ ) with the number of methylenes as previously demonstrated (see Prudencio, A.; Schmeltzer, R.; Uhrich, K. *Macromolecules* **2005**, 38, 6895-6901). Glass transition temperatures ( $T_g$ ) increased with the number of methoxy groups in the aromatic ring due to the decreased flexibility of the polymer chains. This trend of methoxy substitution on aromatic rings increasing the glass  
30 transition temperature ( $T_g$ ) by a chain stiffening effect has been observed in polyesters containing methoxy-substituted aromatic rings.

							
Polymer	R	n	Cmpd. (%)	Contact Angle (°)	T <sub>g</sub> (°C)	T <sub>d</sub> (°C)	Molecular Weight
1a	H, vanillic acid	4	75.3	60	59	268	63100
1b	H, vanillic acid	8	66.9	71	37	325	88800
1c	OCH <sub>3</sub> , syringic acid	4	78.3	60	86	289	12500
1d	OCH <sub>3</sub> , syringic acid	8	70.5	75	79	335	34300

**Table 1.** Properties of phenolic derivative-based poly(anhydride-esters) **1a-d**.

### Example 2.

#### Degradation Studies.

5        *Sample preparation.* Polymer pellets were prepared by pressing ground polymers ( $\sim 150 \pm 5$  mg) into 13 mm diameter x 1 mm thick disks in an IR pellet die (International Crystal Laboratories, Garfield, NJ) with a bench-top hydraulic press (Carver model M, Wabash, IN]. A pressure of 5,000 psi was applied for 5 min at room temperature. No change in polymer color was observed upon  
10        applying pressure.

*Degradation media preparation.* Degradation media consisted of phosphate buffer solution (PBS) containing 0.1 M potassium hydrogen phosphate and 0.1 M potassium dihydrogen phosphate. The pH was adjusted to 7.4 with 1 M sodium hydroxide and/or 1 N hydrochloric acid solutions and pH-  
15        measurements were performed on an Accumet® AR15 pH-meter (Fisher Scientific, Fair Lawn, NJ).

*In vitro hydrolytic degradation.* Hydrolytic degradation of the polymers was performed by placing the disks in 20 mL Wheaton glass scintillation vials (Fisher, Fair Lawn, NJ) with 10 mL of PBS, and incubating them at 37 °C with  
20        agitation using a controlled environment incubator-shaker (New Brunswick



Scientific Co., Edison, NJ) at 60 rpm for 8 days. The buffer solution was replaced by fresh solution (10 mL) after 2, 4, 8, and 24 h of incubation and then every 24 h. The spent media was analyzed by HPLC to determine the concentration of free vanillic acid (VA) and syringic acid (SGA) in solution at each time point and by UV to follow polymer degradation. Data (average of 3 samples per time point) were plotted into cumulative percent-time curves.

*Free biologically active compound determination.* Vanillic acid (VA) and syringic acid (SGA) contents in the degradation media were determined chromatographically by a Perkin-Elmer HPLC system consisting of a Series 200 quaternary LC pump, and an ISS 200 autosampler, on a Zorbax C-8 reverse-phase column (4.6 x 150 mm) at 25 °C using a mixture of methanol:DDW:TFA 50:49.05:0.05 v/v/v as mobile phase at a flow rate of 1.0 mL/min. A 785A absorbance detector set at 251 nm was used to detect vanillic acid (VA) and at 261 nm to detect syringic acid (SGA). A Dell OptiPlex GX110 computer running Perkin-Elmer TurboChrom 4 software was used for data collection and processing, and to automate the analysis via Perkin-Elmer Nelson 900 Series Interface and 600 Series Link. Free phenolic compound concentration in the degradation media was determined from standard curves generated with solutions of known concentrations ( $2.5 \times 10^{-4}$ - $1.1 \times 10^{-1}$  mg/mL). Degradation media was filtered through 0.45  $\mu$ m poly(tetrafluoroethylene) (PTFE) syringe filters (Whatman, Clifton, NJ) before elution.

*Polymer degradation.* UV spectroscopy ( $\lambda$ =251 and 261 nm, for VA and SGA, respectively) with a DÜ 520 UV/vis spectrophotometer (Beckman Instruments, Fullerton, CA) was used to follow polymer degradation by measuring phenolic compound concentration in any form of degradation product. UV data were calibrated against vanillic acid and syringic acid solutions of known concentrations ( $5.7 \times 10^{-4}$ - $1.2 \times 10^{-1}$  mg/mL).

**Polymer Hydrolytic Degradation.** The hydrolytic degradation of phenolic derivative-based poly(anhydride-esters) was investigated on polymer disks immersed in pH 7.4 phosphate buffered solution at 37 °C for 5-8 days. Free phenolic derivative concentration in the degradation media at each time

point was determined by HPLC and polymer degradation was followed by UV spectrometry. For polymer degradation to occur, water must penetrate into the matrix. Once water has penetrated into the matrix, anhydride and ester bonds are broken and solubilization of the degradation products becomes another critical

5 step in the degradation/hydrolysis. The hydrolytic degradation of phenolic derivative-based poly(anhydride-esters) (**1**) initially yielded small oligomers and the monomer precursor or diacid (**5**) upon cleavage of the anhydride bonds. The diacid (**5**) further breaks into the phenolic derivative (**2**) and a carboxylic acid (**3**) *via* ester bond cleavage as confirmed by HPLC. HPLC chromatograms The

10 retention times were 2.8 min and 2.9 min for vanillic acid (VA) and syringic acid (SGA), respectively. Cumulative percent of VA and SGA released in their free form at each time point during the degradation are presented in Figure 1. Over the 5-8 day degradation period, cumulative release of SGA and VA in their free form ranged from 1.0-4.7 %. The rest was accounted for vanillic acid and

15 syringic acid in the form of diacid and/or small oligomers. The solubilities of the degradation products explain the amount of phenolic derivative in its free form detected in solution at each time point (Figure 1). Based on the solubilities of vanillic acid (47 mg/mL) and syringic acid (56 mg/mL) in PBS, diacids and oligomers based on syringic acid are more soluble in the degradation media

20 (PBS) than their analogues based on vanillic acid. The higher the solubility of the degradation products (oligomers and diacids), the more of these compounds will go in solution before breaking down into free phenolic derivative, yielding a lower concentration of phenolic derivative detected in solution. The polymers based on vanillic acid **1a** and **1b** released the higher amounts of phenolic

25 derivative in solution, 1.9 % and 4.7 %, respectively, due to the lower solubility of the polymer degradation products as compared to those based on syringic acid. The lower amounts of free syringic acid detected in solution from the polymers **1c-d** degradation is explained by the higher solubility of the corresponding diacids and/or small oligomers. decreased as the solubility of the other

30 degradation products (diacids and small oligomers) increased.

Polymer hydrophobicity/hydrophilicity is a good indicator of *in vitro* degradation rate as a factor that influences water penetration into the polymer matrix. Static contact angles of phosphate buffer solution (PBS) on the polymer disks surfaces ranging from 60 to 75 ° were measured to determine polymer hydrophobicity (Table 1). Polymer degradation rates were determined by UV measurements (Figure 2) and decreased with higher contact angles (more hydrophobic). Indeed, polymer **1d** displayed the highest contact angle value (75 °) and also displayed the slowest degradation relative to the other poly(anhydride-esters) (**1a-c**). For the polymers **1a** and **1c** that had the same contact angles, the faster degradation rate of **1a** is explained by the faster solubilization of the polymer degradation products. Polymer degradation rates (Figure 2), determined by UV measurements, correlated with the solubility of vanillic (47 mg/mL) and syringic acid (56 mg/ mL) in the degradation media (PBS) and contact angles. Polymers with the lowest contact angles were the fastest degrading , increasing with higher solubility. The amount of phenolic derivative in its free form detected in solution at each time point (Figure 1) decreased as the solubility of the other degradation products (diacids and small oligomers) increased. Polymer degradation rates (Figure 1), determined by HPLC measurements, correlated with the solubility of vanillic (47 mg/mL) and syringic acid (56 mg/ mL) in the degradation media (PBS).

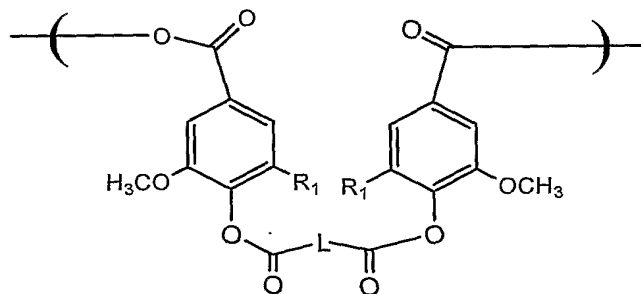
All publications, patents, and patent documents are incorporated by reference herein, as though individually incorporated by reference. The invention has been described with reference to various specific and preferred embodiments and techniques. However, it should be understood that many variations and modifications may be made while remaining within the spirit and scope of the invention.

## CLAIMS

What is claimed is:

1. A composition suitable for topical administration to an animal comprising a polyanhydride having a backbone that degrades within 60 hours of administration to provide a biologically active compound.
2. The composition of claim 1 that further comprises a dermatologically acceptable carrier.
3. The composition of claim 1 which comprises an antioxidant, antiseptic, or antibacterial agent.
4. The composition of claim 3 wherein the antioxidant, antiseptic, or antibacterial agent is a hydroxy aryl carboxylic acid.
5. The composition of claim 3 wherein the antioxidant, antiseptic, or antibacterial agent is selected from vanillic acid, syringic acid, *p*-coumaric acid, caffeic acid, gallic acid, ferulic acid, sinapic acid, protocatechuic acid, and *p*-hydroxybenzoic acid.
6. The composition of claim 3 wherein the antioxidant, antiseptic, or antibacterial agent is dispersed in the matrix of the polyanhydride.
7. The composition of claim 3 wherein the antioxidant, antiseptic, or antibacterial agent is appended to the polyanhydride.
8. The composition of any one of claims 3-7 wherein the antioxidant, antiseptic, or antibacterial agent is incorporated into the backbone of the polyanhydride.
9. The composition of any one of claims 1-8 which comprises microspheres that comprise the polyanhydride.
10. The composition of any one of claims 1-9 wherein the polyanhydride degrades within 48 hours of administration.
11. The composition of any one of claims 1-9 wherein the polyanhydride degrades within 36 hours of administration.
12. The composition of any one of claims 1-9 wherein the polyanhydride degrades within 24 hours of administration.
13. The composition of any one of claims 1-9 wherein the polyanhydride degrades within 18 hours of administration.

14. A composition suitable for topical administration comprising microspheres that degrade within 60 hours of administration, the microspheres comprising a polyanhydride having a backbone that comprises a hydroxy aryl carboxylic acid.
15. The composition of claim 14 wherein the microspheres degrade within 24 hours of administration.
16. The composition of claim 14 wherein the polyanhydride backbone comprises one or more groups that will provide vanillic acid, syringic acid, *p*-coumaric acid, caffeic acid, gallic acid, ferulic acid, sinapic acid, protocatechuic acid, or *p*-hydroxybenzoic acid upon hydrolysis of the backbone.
17. The composition of any one of claims 1-16 wherein the polyanhydride comprises one or more units of the following formula:



wherein:

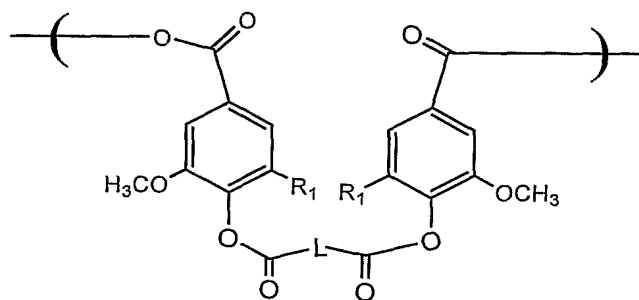
each R<sub>1</sub> is independently H, or methoxy; and

L is a divalent, branched or unbranched, saturated or unsaturated, hydrocarbon chain, having from 1 to 20 carbon atoms, wherein the chain is optionally substituted on carbon with one or more (e.g. 1, 2, 3, or 4) substituents selected from the group consisting of (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, (C<sub>1</sub>-C<sub>6</sub>)alkanoyl, (C<sub>1</sub>-C<sub>6</sub>)alkanoyloxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxycarbonyl, (C<sub>1</sub>-C<sub>6</sub>)alkylthio, azido, cyano, nitro, halo, hydroxy, oxo, carboxy, aryl, aryloxy, heteroaryl, and heteroaryloxy.

18. The composition of claim 17 wherein L is a divalent, branched or unbranched, saturated or unsaturated, hydrocarbon chain, having from 1 to 20 carbon atoms, wherein one or more (e.g. 1, 2, 3, or 4) of the carbon atoms is optionally replaced by (-O-) or (-NR-).

19. The composition of claim 17 wherein L is a divalent, branched or unbranched, saturated or unsaturated, hydrocarbon chain, having from 3 to 15 carbon atoms, wherein one or more (e.g. 1, 2, 3, or 4) of the carbon atoms is optionally replaced by (-O-) or (-NR-), and wherein the chain is optionally substituted on carbon with one or more (e.g. 1, 2, 3, or 4) substituents selected from the group consisting of (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, (C<sub>1</sub>-C<sub>6</sub>)alkanoyl, (C<sub>1</sub>-C<sub>6</sub>)alkanoyloxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxycarbonyl, (C<sub>1</sub>-C<sub>6</sub>)alkylthio, azido, cyano, nitro, halo, hydroxy, oxo, carboxy, aryl, aryloxy, heteroaryl, and heteroaryloxy.
20. The composition of claim 17 wherein L is a divalent, branched or unbranched, saturated or unsaturated, hydrocarbon chain, having from 3 to 15 carbon atoms, wherein one or more (e.g. 1, 2, 3, or 4) of the carbon atoms is optionally replaced by (-O-) or (-NR-).
21. The composition of claim 17 wherein L is a divalent, branched or unbranched, saturated or unsaturated, hydrocarbon chain, having from 3 to 15 carbon atoms.
22. The composition of claim 17 wherein L is a divalent, branched or unbranched, hydrocarbon chain, having from 4 to 8 carbon atoms.
23. The composition of claim 17 wherein L is -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-.
24. The composition of any one of claims 17-23 wherein each R<sub>1</sub> is H.
25. The composition of any one of claims 17-23 wherein each R<sub>1</sub> is methoxy.
26. A method for promoting an antioxidant, antiseptic, or antibacterial effect comprising topically administering the composition of any one of claim 3-8 to an animal.
27. A method for administering a biologically active compound to an animal comprising topically applying to the animal a composition that comprises a polyanhydride having a backbone that degrades within 60 hours of applying to provide the biologically active compound.
28. The method of claim 27 wherein the composition further comprises a dermatologically acceptable carrier.
29. The method of claim 27 wherein the composition comprises an antioxidant, antiseptic, or antibacterial agent.

30. The method of claim 29 wherein the antioxidant, antiseptic, or antibacterial agent is a hydroxy aryl carboxylic acid.
31. The method of claim 29 wherein the antioxidant, antiseptic, or antibacterial agent is selected from vanillic acid, syringic acid, *p*-coumaric acid, caffeic acid, gallic acid, ferulic acid, sinapic acid, protocatechuic acid, and *p*-hydroxybenzoic acid.
32. The method of claim 29 wherein the antioxidant, antiseptic, or antibacterial agent is dispersed in the matrix of the polyanhydride.
33. The method of claim 29 wherein the antioxidant, antiseptic, or antibacterial is appended to the polyanhydride.
34. The method of claim 29 wherein wherein the antioxidant, antiseptic, or antibacterial agent is incorporated into the backbone of the polyanhydride.
35. The method of claim 27 wherein the composition comprises microspheres that comprise the polyanhydride.
36. The method of any one of claims 27-35 wherein the polyanhydride degrades within 48 hours of administration.
37. The method of any one of claims 27-35 wherein the polyanhydride degrades within 36 hours of administration.
38. The method of any one of claims 27-35 wherein the polyanhydride degrades within 24 hours of administration.
39. The method of any one of claims 27-35 wherein the polyanhydride degrades within 18 hours of administration.
40. A composition as described in any one of claims 1-26 for use in medical therapy.
41. The use of a composition as described in any one of claims 3-8 and 16-25 to prepare a medicament for promoting an antioxidant, antiseptic, or antibacterial effect when administered to a mammal.
42. A polyanhydride comprises units of the following formula (I):



wherein:

each  $R_1$  is independently H, or methoxy; and

L is a divalent, branched or unbranched, saturated or unsaturated, hydrocarbon chain, having from 1 to 20 carbon atoms, wherein the chain is optionally substituted on carbon with one or more (e.g. 1, 2, 3, or 4) substituents selected from the group consisting of (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, (C<sub>1</sub>-C<sub>6</sub>)alkanoyl, (C<sub>1</sub>-C<sub>6</sub>)alkanoyloxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxycarbonyl, (C<sub>1</sub>-C<sub>6</sub>)alkylthio, azido, cyano, nitro, halo, hydroxy, oxo, carboxy, aryl, aryloxy, heteroaryl, and heteroaryloxy.

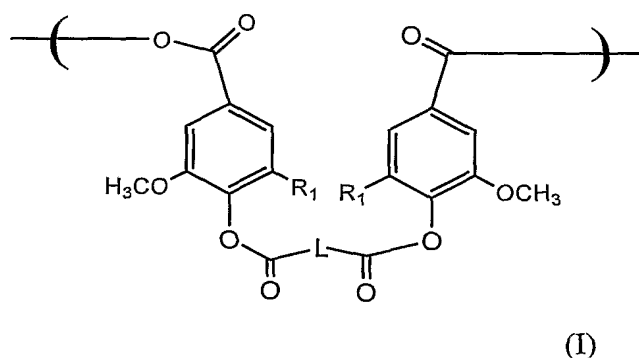
43. The polyanhydride of claim 42 wherein L is a divalent, branched or unbranched, saturated or unsaturated, hydrocarbon chain, having from 1 to 20 carbon atoms, wherein one or more (e.g. 1, 2, 3, or 4) of the carbon atoms is optionally replaced by (-O-) or (-NR-).

44. The polyanhydride of claim 42 wherein L is a divalent, branched or unbranched, saturated or unsaturated, hydrocarbon chain, having from 3 to 15 carbon atoms, wherein one or more (e.g. 1, 2, 3, or 4) of the carbon atoms is optionally replaced by (-O-) or (-NR-), and wherein the chain is optionally substituted on carbon with one or more (e.g. 1, 2, 3, or 4) substituents selected from the group consisting of (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, (C<sub>1</sub>-C<sub>6</sub>)alkanoyl, (C<sub>1</sub>-C<sub>6</sub>)alkanoyloxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxycarbonyl, (C<sub>1</sub>-C<sub>6</sub>)alkylthio, azido, cyano, nitro, halo, hydroxy, oxo, carboxy, aryl, aryloxy, heteroaryl, and heteroaryloxy.

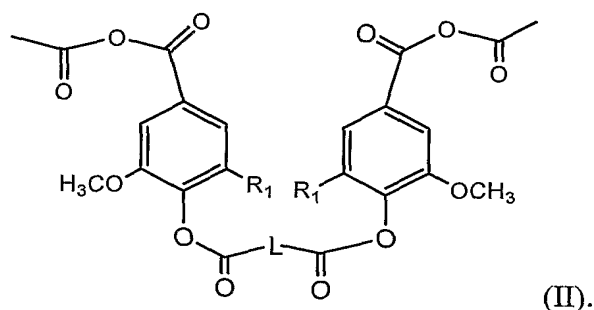
45. The polyanhydride of claim 42 wherein L is a divalent, branched or unbranched, saturated or unsaturated, hydrocarbon chain, having from 3 to 15 carbon atoms, wherein one or more (e.g. 1, 2, 3, or 4) of the carbon atoms is optionally replaced by (-O-) or (-NR-).



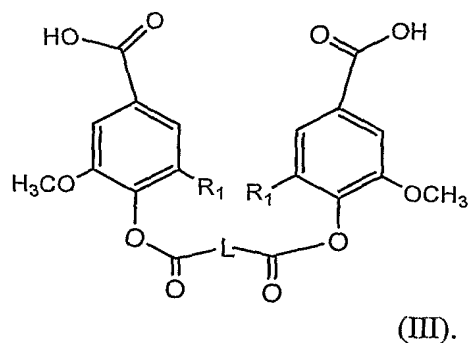
46. The polyanhydride of claim 42 wherein L is a divalent, branched or unbranched, saturated or unsaturated, hydrocarbon chain, having from 3 to 15 carbon atoms.
47. The polyanhydride of claim 42 wherein L is a divalent, branched or unbranched, hydrocarbon chain, having from 4 to 8 carbon atoms.
48. The polyanhydride of claim 42 wherein L is  $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$ .
49. The polyanhydride of any one of claims 42-47 wherein each  $\text{R}_1$  is H.
50. The polyanhydride of any one of claims 42-47 wherein each  $\text{R}_1$  is methoxy.
51. A method for preparing a polyanhydride of formula (I):



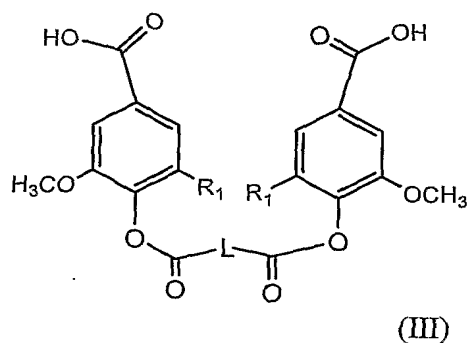
as described in claim 17 comprising polymerizing a corresponding compound of formula (II):



52. The method of claim 51 wherein the polymerization is carried out by melt condensation.
53. A method for preparing a compound of formula (II) as described in claim 51 comprising acylating a corresponding diacid of formula (III):



54. A compound of formula (III):



wherein:

each  $R_1$  is independently H, or methoxy; and

L is a divalent, branched or unbranched, saturated or unsaturated, hydrocarbon chain, having from 1 to 20 carbon atoms, wherein the chain is optionally substituted on carbon with one or more (e.g. 1, 2, 3, or 4) substituents selected from the group consisting of (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, (C<sub>1</sub>-C<sub>6</sub>)alkanoyl, (C<sub>1</sub>-C<sub>6</sub>)alkanoyloxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxycarbonyl, (C<sub>1</sub>-C<sub>6</sub>)alkylthio, azido, cyano, nitro, halo, hydroxy, oxo, carboxy, aryl, aryloxy, heteroaryl, and heteroaryloxy.

55. The compound of claim 54 wherein L is a divalent, branched or unbranched, saturated or unsaturated, hydrocarbon chain, having from 1 to 20 carbon atoms, wherein one or more (e.g. 1, 2, 3, or 4) of the carbon atoms is optionally replaced by (-O-) or (-NR-).

56. The compound of claim 54 wherein L is a divalent, branched or unbranched, saturated or unsaturated, hydrocarbon chain, having from 3 to 15 carbon atoms, wherein one or more (e.g. 1, 2, 3, or 4) of the carbon atoms is optionally replaced by (-O-) or (-

NR-), and wherein the chain is optionally substituted on carbon with one or more (e.g. 1, 2, 3, or 4) substituents selected from the group consisting of (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, (C<sub>1</sub>-C<sub>6</sub>)alkanoyl, (C<sub>1</sub>-C<sub>6</sub>)alkanoyloxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxycarbonyl, (C<sub>1</sub>-C<sub>6</sub>)alkylthio, azido, cyano, nitro, halo, hydroxy, oxo, carboxy, aryl, aryloxy, heteroaryl, and heteroaryloxy.

57. The compound of claim 54 wherein L is a divalent, branched or unbranched, saturated or unsaturated, hydrocarbon chain, having from 3 to 15 carbon atoms, wherein one or more (e.g. 1, 2, 3, or 4) of the carbon atoms is optionally replaced by (-O-) or (-NR-).

58. The compound of claim 54 wherein L is a divalent, branched or unbranched, saturated or unsaturated, hydrocarbon chain, having from 3 to 15 carbon atoms.

59. The compound of claim 54 wherein L is a divalent, branched or unbranched, hydrocarbon chain, having from 4 to 8 carbon atoms.

60. The compound of claim 54 wherein L is -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-.

61. The compound of any one of claims 54-60 wherein each R<sub>1</sub> is H.

62. The compound of any one of claims 54-60 wherein each R<sub>1</sub> is methoxy.

63. A method for promoting an antioxidant, antiseptic, or antibacterial effect comprising topically administering the compound of any one of claims 54-60 or a pharmaceutically acceptable salt thereof to a mammal.

64. A compound as described in any one of claims 54-61 or a pharmaceutically acceptable salt thereof for use in medical therapy.

65. The use of a compound as described in any one of claims 54-61 or a pharmaceutically acceptable salt thereof to prepare a medicament for promoting an antioxidant, antiseptic, or antibacterial effect when administered to an animal.

Figure 1

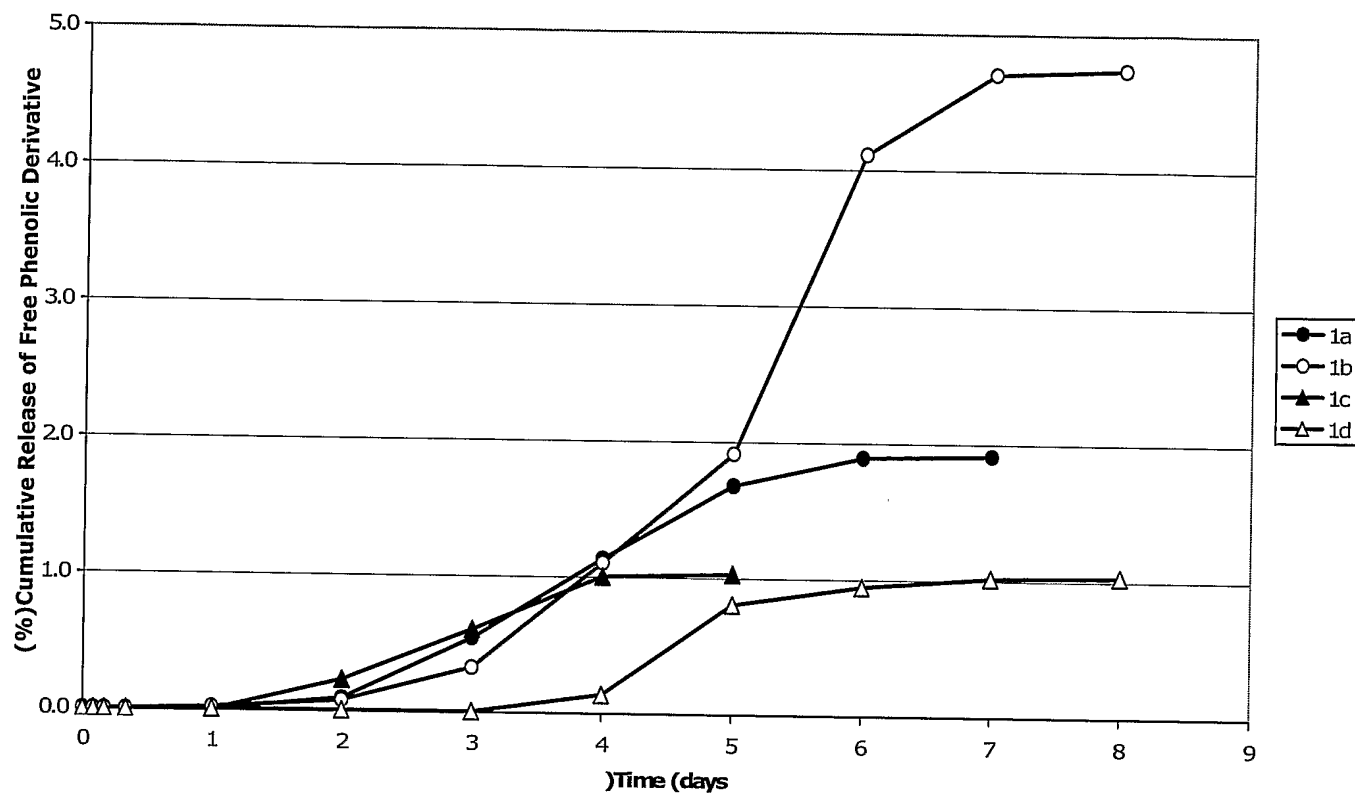


Figure 2

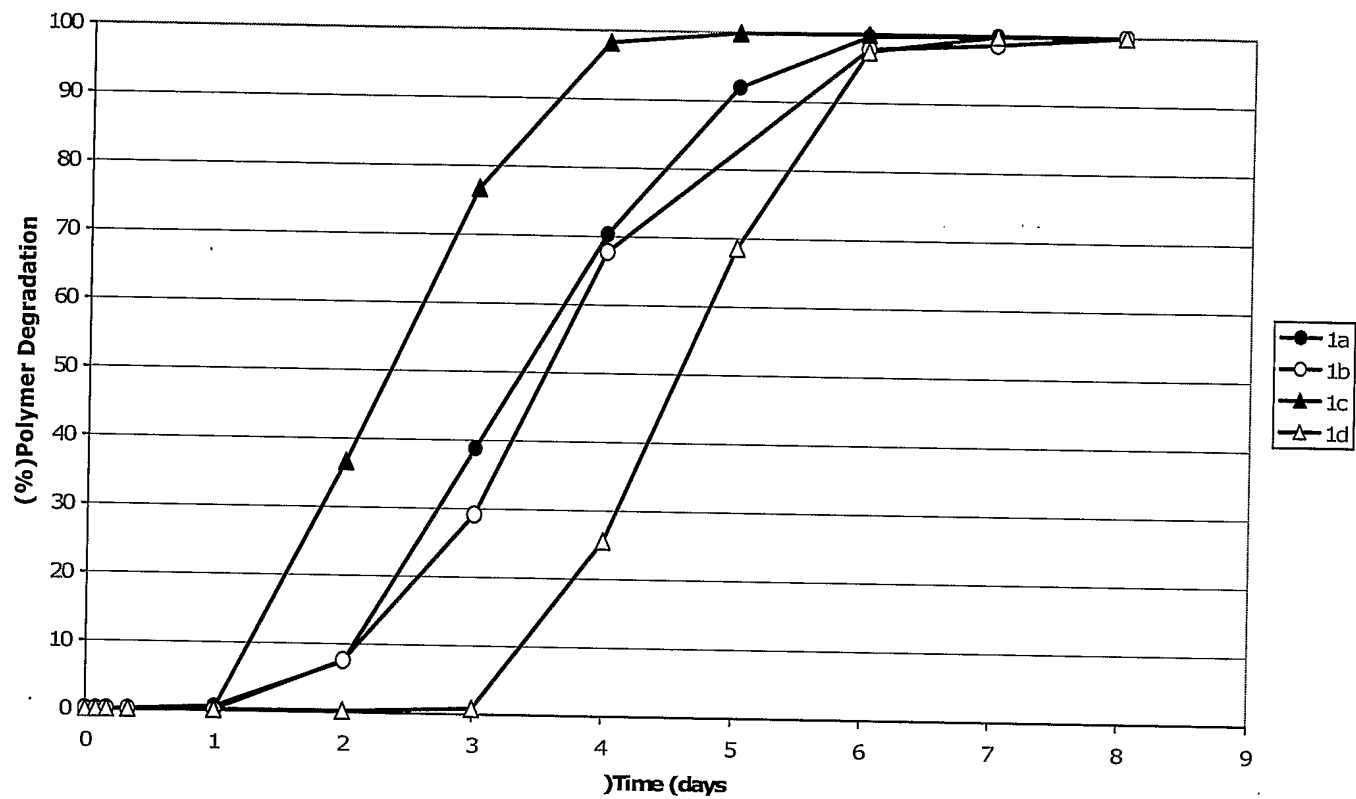


Figure 3

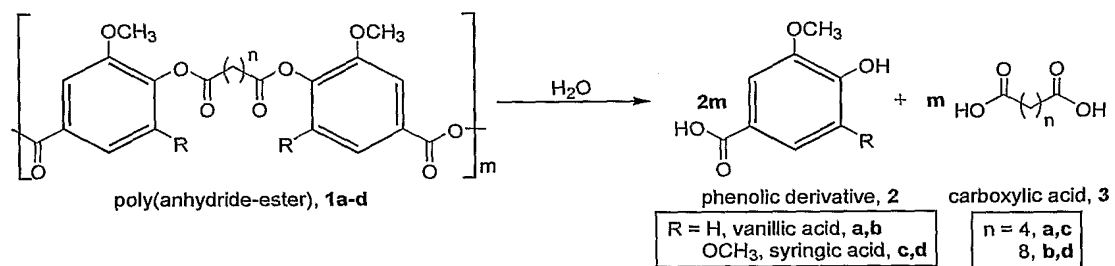
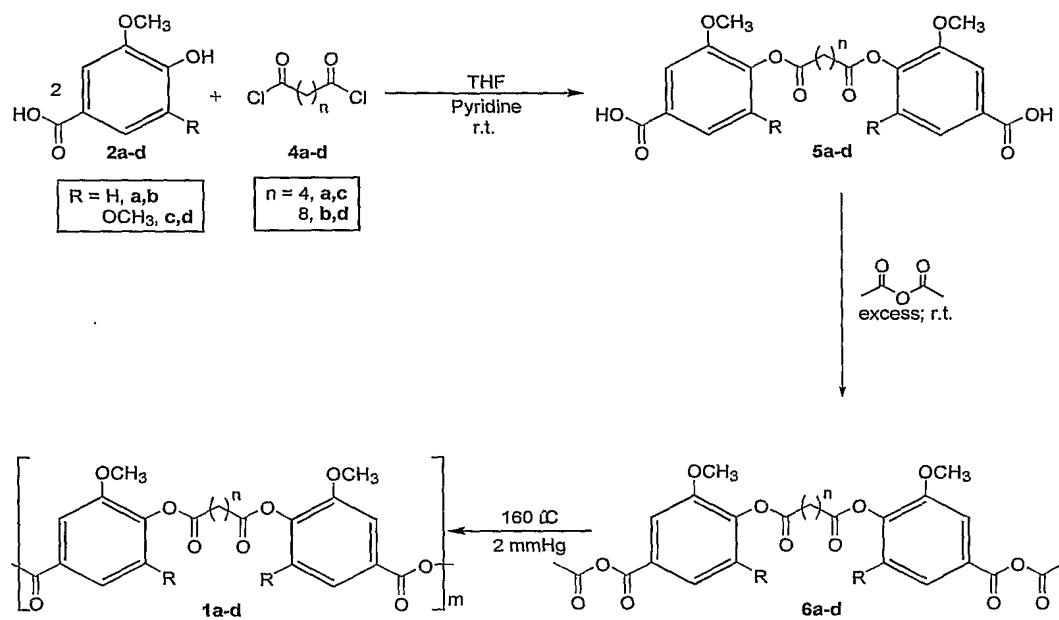


Figure 4



# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US06/19848

## A. CLASSIFICATION OF SUBJECT MATTER

IPC: A61F 2/00( 2006.01)

USPC: 424/484

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/484

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Nagata. M. Synthesis, Characterization and Hydrolytic Degradation of Copolymers of 3-(4-Hydroxyphenyl) propionic Acid and p-Hydroxybenzoic Acid, Vanilic Acid, or Syringic Acid J. Appl Polym. Sci. December 2000, Vol 78. No. 14, pages 2474-2481, especially page 2474-2475.	1-8,10-13,27-34,36-40
P,Y	Fan. J. et al. The Effect of Substitution Levels on the Luminescent and Degradation Properties of Fluorescent Poly(ester-anhydride)s J. Appl. Polym. Sci. April 2006, Vol 100 No. 2, pages 1214-1221, especially pages 1214-1217.	1-65
Y	Ulrich. K.E. et al. Polymeric Systems for Controlled Release Chem. Rev. October 1999, Vol 99. No. 11, pages 3181-3198, especially pages 3181-3183 and 3193-3194.	1



Further documents are listed in the continuation of Box C.



See patent family annex.

\* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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"X"

document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y"

document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

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Date of the actual completion of the international search

07 September 2006 (07.09.2006)

Date of mailing of the international search report

29 SEP 2006

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